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Predictive value of progesterone receptor in advanced-stage breast cancer patients treated with CDK 4/6 inhibitors

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ABSTRACT

Aims: Phase III studies investigating CDK 4/6 inhibitors have failed to identify significant predictive or prognostic markers that aid clinicians in therapeutic decision-making. Given the complex treatment landscape in breast cancer, identifying patient and tumor characteristics that optimize the utilization of CDK 4/6 inhibitors across diverse therapeutic approaches is crucial. In our study, we aimed to evaluate the predictive role of progesterone receptor (PR) expression levels in patients with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced-stage breast cancer treated with CDK 4/6 inhibitors.

Methods: This study retrospectively evaluated 244 patients who received a combination of CDK 4/6 inhibitors and endocrine therapy as their first-line treatment. Those with PR levels below 20% were designated as low PR expression patients, and those with levels of 20% or above were classified as high PR expression patients. These two groups were compared in terms of demographic characteristics and progression-free survival (PFS).

Results: Progression events occurred in 37 of 83 patients in the low PR expression group and 55 of 161 patients in the high PR expression group. Patients with low PR expression demonstrated a significantly shorter median PFS of 23.13 months (95% CI, 15.67-30.59) compared to those with high PR expression, who exhibited a median PFS of 34.66 months (95% CI, 24.27-45.05) (p=0.002). This significant difference in mPFS was observed consistently across both ribociclib (p=0.034) and palbociclib (p=0.024) treatment groups.

Conclusion: This study suggests that PR expression may also predict disease progression in patients initiating CDK 4/6 inhibitors and endocrine therapy in addition to ER levels. While these findings are promising, further research is warranted to validate them in more extensive, prospective studies.

Keywords: Advanced stage breast cancer, biomarker, CDK 4/6 inhibitors, endocrine therapy, progesterone receptor

INTRODUCTION

Breast cancer is a heterogeneous disease with various molecular subtypes and biological characteristics. The main subtypes of breast cancer can be identified by immunohistochemical (IHC) markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These subtypes of breast cancer have different treatment strategies and clinical implications.

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recommend routine assessment of both ER and PR status in all invasive breast cancer.[1] This information should be used to guide patient selection for endocrine therapy (ET), as clinical trials have demonstrated that PR positivity, independent of ER status, is predictive of ET response.[1]

A tumor's likelihood of responding to ET is a critical factor in breast cancer management. However, not all patients with breast cancer benefit from ET. Expression of ER or PR is considered the most reliable predictor of which patients are most likely to benefit from ET.

ER expression predicts which patients will benefit from ET. While patients with PR-positive tumors also experience improved outcomes with ET, PR is considered a functional indicator of the ER pathway.[2] It is established that PR status can divide ER-positive tumors into different prognostic categories. Evidence suggests that PR positivity, independent of ER status, predicts ET response, and it is recommended that PR be considered when making ET decisions for patients.[3]

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In first-line treatment of advanced-stage breast cancer (ABC) in women with hormone receptor (HR)-positive HER2-negative status, pivotal trials with cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors (ribociclib, palbociclib, and abemaciclib) have shown significant improvements in progression-free survival (PFS).[4-6] Based on these results, current guidelines recommend the combination of CDK 4/6 inhibitors with ET as first-line treatment in this patient population.

The subgroup analyses of phase III studies on CDK 4/6 inhibitors have not identified any robust predictive or prognostic markers that could assist clinicians in determining therapeutic selection.[7] Considering the complexity of these treatments, it is essential to identify patient and tumor characteristics that could help determine when and in which treatment paradigms CDK 4/6 inhibitors should be used.[8]

Studies examining the predictive significance of PR for CDK 4/6 inhibitors are rare and controversial. Additionally, threshold values for PR to predict prognosis or treatment have yet to be thoroughly investigated. Real-world data can help clarify ongoing debates and guide optimal management in routine clinical practice.

Our study aimed to evaluate the predictive role of PR expression levels in patients with ABC ER-positive/HER2-negative receiving CDK 4/6 inhibitors.

METHODS

This retrospective study included all eligible patients who presented to our center between June 2017 and July 2023. As this was a retrospective study, and the sample size was determined by the number of eligible patients identified during the study period, a formal power analysis was not performed. This retrospective study was conducted in accordance with recognized ethical standards, including the principles of the Declaration of Helsinki, and received approval from the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.02.2024, Decision No: 2024-02/04). The Ethics Committee waived the requirement for informed consent, as the study was retrospective and non-interventional, and deemed that obtaining consent was unnecessary in accordance with national regulations.

Based on the number of eligible patients treated at our center in recent years, we initially estimated that we could include approximately 300 patients. However, after applying the exclusion criteria, the final sample size comprised 244 patients with ABC ER-positive/HER2-negative who received first-line treatment with ribociclib or palbociclib in combination with ET, including letrozole or fulvestrant. Amebaciclib, not covered under reimbursement in our country, was not a preferred treatment option. The pathological evaluation was performed according to the ASCO/CAP guidelines. ER, PR and HER2 were evaluated using IHC. The PR IHC evaluation was performed by a single experienced pathologist, and no second observer review was conducted. Inclusion criteria were as follows: being female over 18 years of age, having de novo or recurrent metastatic breast cancer, having an ER level of 10% or higher, having a PR level assessed in the pathology report, having a HER2 score of 0 and 1+ or 2+ by IHC method and negative by in situ hybridization (ISH) method, receiving CDK 4/6 inhibitor plus ET treatment in the first-line setting, having adequate organ functions, and having an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Exclusion criteria included being pregnant, breastfeeding, or having male breast cancer, having early-stage breast cancer, having unknown PR levels in pathology reports, having ER levels below 10%, having HER2 IHC scores of 3+ or 2+ with ISH positivity, receiving CDK 4/6 inhibitor plus ET treatment in the second-line or later settings, and having an ECOG PS of 3-4.

For patients with recurrent disease, pathological information, including the percentage of PR expression, was obtained from the relapse biopsy, if available. For patients with de novo disease or without an available relapse biopsy, pathological information, including PR expression, was retrieved from the initial diagnostic biopsy.

According to the St. Gallen guidelines, PR expression and Ki-67 levels were categorized into two groups: less than 20% and 20% or greater.[9] Patients with PR levels below 20% were classified as having low PR expression, while those with 20% and above were classified as having high PR expression. These two groups were compared in terms of PFS. Patients with a HER2 IHC score of 0 were classified into the HER2 negative group, while those with a HER2 IHC score of 1 and those with a score of 2 but negative ISH were included in the HER2 low group. Patient files were retrospectively screened using the hospital archive system and the automation recording system for median age, menopausal status, presence of any comorbid diseases, tumor grade, Ki-67 levels, administration of ribociclib or palbociclib, concurrent use of letrozole or fulvestrant, presence of visceral or non-visceral metastases, and whether the disease was de novo or recurrent.

Endocrine resistance was defined according to the fourth ESO-ESMO International Consensus guidelines. Primary endocrine resistance was defined as disease progression within the first six months of first-line ET for metastatic breast cancer or recurrence within the first two years of adjuvant ET. Secondary endocrine resistance was defined as recurrence during adjuvant ET but after the first two years, recurrence within 12 months of completing adjuvant ET, or disease progression after six months of initiating ET for metastatic breast cancer.[10]

Patients with de novo metastatic disease or without acquired resistance received a CDK 4/6 inhibitor combined with letrozole. Patients who developed primary or secondary resistance while on adjuvant therapy were treated with a CDK 4/6 inhibitor and fulvestrant.

Ribociclib at a dose of 600 mg or palbociclib at 125 mg was initiated in cycles of 28 days, with 21 days of treatment followed by a 7-day break. Concomitant ET consisted of 2.5 mg of letrozole daily or 500 mg of fulvestrant administered intramuscularly every 28 days. Additionally, luteinizing hormone-releasing hormone analog was added to the treatment regimen of pre/perimenopausal patients. Patients

with bone metastases were treated with zoledronic acid or denosumab if there were no contraindications.

PFS is the time from initiating CDK 4/6 inhibitors plus ET treatment to disease progression, death, or the last medical record. Overall survival (OS) is defined as the time from the start of treatment to death or the date of the last follow-up. During the descriptive statistics, non-parametric variables were presented as median (range), while categorical data were presented as frequency (percentage). The Chi-square test was used to compare categorical data between independent groups. PFS and OS durations were calculated using the Kaplan-Meier method. The median values for PFS were calculated. It was not specified since the median value could not be reached for OS. Independent prognostic factors were determined by creating a Cox Regression model with factors found to be statistically significant ($p<0.05$) using Kaplan Meier. IBM Corp. for statistical analysis. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: The IBM Corp program was used.

RESULTS

Of the 244 patients included in the study, 83 (34.0%) had low PR expression, and 161 (66.0%) had high PR expression. The median age of the patients was 55 (range 25-87 years). Among patients aged ≤55 years (n=116), 36 (43.4%) had low PR expression and 80 (49.7%) had high PR expression, while among patients older than 55 years (n=128), 47 (56.6%) had low PR expression and 81 (50.3%) had high PR expression.

Low PR expression was detected in 39 (47.0%) of the patients with visceral metastasis (n=92), and high PR expression in 53 (32.9%). In comparison, low PR expression was detected in 44 (53.0%) of the patients with non-visceral metastasis (n=152) and high PR expression in 108 (67.1%) (p=0.032). Low PR expression was detected in 51 (61.4%) patients who received adjuvant ET before CDK 4/6 inhibitor treatment, and high PR expression in 69 (42.9%). In comparison, low PR expression was detected in 32 (38.6%) of the patients who did not receive adjuvant ET, and high PR expression in 92 (57.1%) (p=0.006).

PR percentages were assessed from primary tumor biopsies in 134 patients (54.9%) and recurrence biopsies in 110 patients (45.1%). Low PR expression was detected in 38 (45.8%) of the primary lesion biopsy samples, and high PR expression was observed in 96 (59.6%). In comparison, low PR expression was detected in 45 (54.2%) of the recurrent lesion biopsy samples and high PR expression in 65 (40.4%) (p=0.039). All patients with de novo disease had PR percentages assessed from their primary tumor biopsies. Among patients with recurrent disease, PR percentages were obtained from the primary tumor biopsy in 24 cases (17.9%) and the recurrence biopsy in 110 cases (82.1%).

Additionally, there was no statistically significant difference between patients with low PR expression and those with high PR expression regarding the presence of median age, menopausal status, tumor grade, Ki-67 proliferation index, Her2 status, CDK 4/6 inhibitors agents, adjuvant endocrine agent, and endocrine resistance (**Table 1**).

The median follow-up duration was 20.8 months (95% CI; 20.35-23.89). Median PFS (mPFS) for patients with low PR expression was 23.13 months (95% CI; 15.67-30.59), whereas it was 34.66 months (95% CI; 24.27-45.05) for patients with high PR expression (p=0.002) (**Figure**).

In those with Ki-67 levels ≤ 20%, the median progression-free survival (mPFS) was not estimated (NE), whereas for those with >20% Ki-67 levels, the mPFS was 24.08 months (95% CI, 18.96-29.21; p=0.004). For grade one tumors, mPFS was not estimable (NE), while for grade two tumors, mPFS was 35.61 months (95% CI, NE), and for grade three tumors, mPFS was 24.08 months (95% CI, 19.94-28.23; p=0.030). Patients with visceral metastases had a mPFS of 21.45 months (95% CI, 10.62-32.29), while those with non-visceral disease had an mPFS of 33.05 months (95% CI, 22.69-43.41) (p=0.049). mPFS was NE in patients with pathological assessment from primary lesion biopsies, whereas those with pathological assessment from recurrent lesion biopsies had an mPFS of 23.85 months (95% CI; 19.29-28.41) (p=0.010). Patients who received adjuvant ET before CDK 4/6 inhibitor treatment had an mPFS of 25.66 months (95% CI; 20.48-30.84), while those who did not receive adjuvant ET had an mPFS of 35.61 months (95% CI; 25.52-45.71) (p=0.044).

Additionally, there was no difference in mPFS based on median age, menopausal status, HER2 status, CDK 4/6 inhibitors, endocrine agent combined with CDK 4/6 inhibitors, adjuvant endocrine agent, and endocrine resistance (**Table 2**).

The mOS was not reached. Five-year OS rates based on PR expression were 34.0% in patients with low PR expression and 72.6% in those with high PR expression (p=0.144). Although this difference did not reach statistical significance, it suggests a potential positive impact of high PR expression on OS. The five-year OS rate was 81.5% in patients with a Ki-67 index below 20%, compared to 40.1% in those with a Ki-67 index above 20% (p=0.005). Regarding HER2 status, the five-year OS rate was 57.9% in HER2-low patients and 67.7% in HER2-negative patients (p=0.034; **Table 3**). These findings suggest that both variables may influence long-term survival outcomes.

In patients receiving ribociclib therapy, the mPFS was 35.61 months (95% CI; 25.55-45.68) in those with high PR expression and 23.85 months (95% CI; 12.84-34.86) in those with low PR expression (p:0.034). In patients receiving palbociclib therapy, the mPFS was NE in those with high PR expression and 16.99 months (95% CI; 5.09-28.89) in those with low PR expression (p:0.024).

Significant factors identified in the univariate analysis, including grade, PR status, Ki-67 levels, and new or recurrent disease status, were evaluated by Cox regression analysis.

The grade, PR status, Ki-67 index, and de novo or recurrent disease status were evaluated using Cox regression analysis after being found significant in univariate analysis. It was demonstrated that both low or high expression of PR (HR: 0.60, 95% CI; 0.36-0.98) (p:0.040) are independent predictive factors (**Table 4**).

Table 1. Baseline characteristics of patients with HR-positive/HER2-negative ABC treated with CDK 4/6 inhibitors plus ET

	Total (n=244)	Low PR expression n=83 (34.0%)	High PR expression n=161 (66.0%)	p-value
Median age (years)				0.349
≤55 y	116 (47.5%)	36 (43.4%)	80 (49.7%)	
>55 y	128 (52.5%)	47 (56.6%)	81 (50.3%)	
Menopausal status (%)				0.730
Pre/perimenopause	74 (30.3%)	24 (28.9%)	50 (31.1%)	
Postmenopause	170 (69.7%)	59 (71.1%)	111 (68.9%)	
Grade				0.211
Grade 1	16 (7.5%)	4 (5.6%)	12 (8.4%)	
Grade 2	116 (54.2%)	34 (47.9%)	82 (57.3%)	
Grade 3	82 (38.3%)	33 (46.5%)	49 (34.3%)	
Ki 67 index-%				0.359
≤20%	91 (39.7%)	27 (35.5%)	64 (41.8%)	
>20%	138 (60.3%)	49 (64.5%)	89 (58.2%)	
HER2 status				0.872
HER 2 low	92 (37.9%)	32 (38.6%)	60 (37.5%)	
HER negative	151 (62.1%)	51 (61.4%)	100 (62.5%)	
CDK 4/6 inhibitors				0.358
Ribociclib	168 (68.9%)	54 (65.1%)	114 (70.8%)	
Palbociclib	79 (32.4%)	28 (33.7%)	51 (31.7%)	
Endocrine agent combined with CDK 4/6 inhibitors				0.181
Letrozole	194 (79.5%)	62 (74.7%)	132 (82.0%)	
Fulvestrant	50 (20.5%)	21 (25.3%)	29 (18.0%)	
Metastatic sites				0.032*
Non-visceral	152 (62.3%)	44 (53.0%)	108 (67.1%)	
Visceral	92 (37.7%)	39 (47.0%)	53 (32.9%)	
Biopsy to evaluate PR percentage				0.039*
Primary lesion biopsy	134 (54.9%)	38 (45.8%)	96 (59.6%)	
Recurrent lesion biopsy	110 (45.1%)	45 (54.2%)	65 (40.4%)	
Adjuvant ET				0.006*
Yes	120 (49.2%)	51 (61.4%)	69 (42.9%)	
No	124 (50.8%)	32 (38.6%)	92 (57.1%)	
Adjuvant endocrine agent				0.880
AI	72 (60.0%)	31 (60.8%)	41 (59.4%)	
Tamoxifen	48 (40.0%)	20 (39.2%)	28 (40.6%)	
Endocrine resistance				0.159
Yes	91 (37.3%)	36 (43.4%)	55 (34.2%)	
No	153 (62.7%)	47 (56.6%)	106 (65.8%)	
Type of endocrine resistance				0.134
Primary	17 (18.7%)	4 (11.1%)	13 (23.6%)	
Secondary	74 (81.3%)	32 (88.9%)	42 (76.4%)	

HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, ABC: Advanced-stage breast cancer, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitor, *Significant

DISCUSSION

Following the demonstration of improvement in PFS with CDK 4/6 inhibitors and ET combination in ABC[7], the United States Food and Drug Administration (FDA) has approved all three CDK 4/6 inhibitors.

It is essential to identify patients who will benefit clinically from CDK 4/6 inhibitor treatments, evaluate their tolerability, and assess their impact on quality of life. Sensitivity and resistance mechanisms to CDK 4/6 inhibitors and ET combinations are highly complex. It is known that PR-negative tumors in patients with ER-positive breast cancer

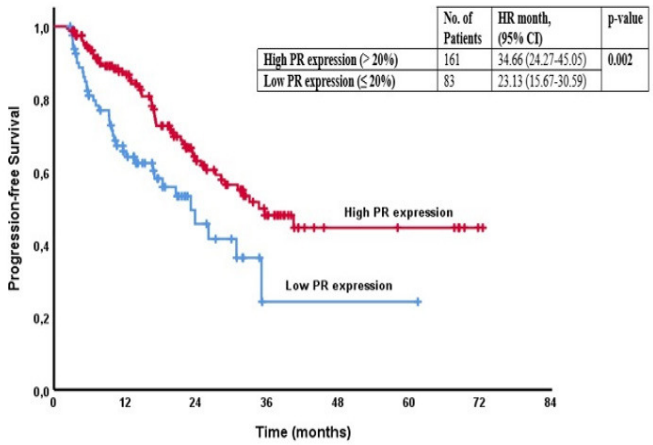

Figure. mPFS curve of low PR expression and high PR expression patients
mPFS: Median progression-free survival, PR: Progesterone receptor, HR: Hormone receptor

are more resistant to ET compared to PR-positive tumors.[11] In recent years, very much evidence has shown that ER-positive/PR-negative tumors exhibit more invasive clinical and pathological characteristics and have a worse prognosis compared to ER-positive/PR-positive tumors.[12] In the 2013 St. Gallen Conference, emphasis was placed on the significant impact of PR loss or low expression (≤20%) on the survival of breast cancer patients.[13]

A study evaluating the impact of PR on metastasis and prognosis in HER2-negative breast cancer patients showed that ER-positive/PR-positive patients had a high incidence of bone metastasis. In contrast, ER-positive/PR-negative patients had a higher incidence of visceral metastasis.[14]

Previous research has identified PR negativity as an independent risk factor for visceral metastasis.[15] Consistent with these findings, our study also revealed that patients with high PR expression exhibited visceral metastasis rates of 32.9%, while the rate of non-visceral disease was 67.1% (p:0.032). A prospective study investigating the predictive role of PR in tamoxifen response in ABC showed that high PR levels are associated with better treatment response, prolonged time to treatment failure, and improvement in OS.[16] Similarly, in another study, PR negativity was shown to be an independent predictive marker for tamoxifen resistance and breast cancer recurrence.[17] Rocca et al.[18] evaluated the impact of PR and Ki-67 levels on the clinical benefit of first-line ET in ABC. In this study, the cut-off value for PR and Ki-67 was determined to be 20%. Patients with PR >20% demonstrated a longer median time to progression (TTP) than those with PR ≤20% (24 months vs. 12 months, p=0.012). In the multivariate analysis, PR was identified as a significant independent determinant of TTP (HR 2.45).

On the contrary, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that tamoxifen improved survival independently of PR status in ER-positive tumors.[2]

Table 2. Progression-free survival rates in patients treated with CDK 4/6 inhibitors plus ET

	PFS median (95% CI)	p-value
Median age (years)		0.566
≤55 y	26.12 (19.08-33.16)	
>55 y	34.66 (24.71-44.61)	
Menopausal status (%)		0.429
Pre/perimenopause	26.12 (18.88-33.36)	
Postmenopause	33.05 (22.02-44.09)	
Grade		0.030*
Grade 1	NE	
Grade 2	35.61 (NE)	
Grade 3	24.08 (19.94-28.23)	
PR status		0.002*
Low PR expression	23.13 (15.67-30.59)	
High PR expression	34.66 (24.27-45.05)	
Ki 67 index-%		0.004*
≤20%	NE	
>20%	24.08 (18.96-29.21)	
HER2 status		0.669
HER 2 low	28.85 (18.06-39.64)	
HER negative	31.05 (23.47-38.63)	
CDK 4/6 inhibitors		0.284
Ribociclib	33.05 (26.77-39.33)	
Palbociclib	26.12 (19.12-33.12)	
Endocrine agent combined with CDK 4/6 inhibitors		0.090
Letrozole	33.05 (26.62-39.49)	
Fulvestrant	21.72 (15.62-27.82)	
Metastatic sites		0.049*
Non-visceral	33.05 (22.69-43.41)	
Visceral	21.45 (10.62-32.29)	
Biopsy to evaluate PR percentage		0.010*
Primary lesion biopsy	NE	
Recurrent lesion biopsy	23.85 (19.29-28.41)	
Adjuvan ET		0.044*
No	35.61 (25.52-45.71)	
Yes	25.66 (20.48-30.84)	
Adjuvant endocrine agent		0.525
AI	23.85 (15.27-32.43)	
Tamoxifen	24.08 (19.77-28.39)	
Endocrine resistance		0.123
Yes	26.12 (18.25-33.99)	
No	35.09 (25.33-44.85)	
Type of endocrine resistance		0.950
Primary	20.24 (10.55-29.93)	
Secondary	27.34 (18.24-36.43)	

HER2: Human epidermal growth factor receptor 2, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitör, NE: Non-estimated,*Significant

Table 3. Overall survival rates in patients treated with CDK 4/6 inhibitors plus ET

	5-year OS	p-value
Median age (years)		0.370
≤55 y	55.9%	
>55 y	74.8%	
Menopausal status (%)		0.908
Pre/perimenopause	34.3%	
Postmenopause	71.7%	
Grade		0.117
Grade 1	NE	
Grade 2	60.4%	
Grade 3	65.7%	
PR status		0.144
Low PR expression	34.0%	
High PR expression	72.6%	
Ki 67 index-%		0.005*
≤20%	81.5%	
>20%	40.1%	
HER2 status		0.034*
HER 2 low	57.9%	
HER negative	67.7%	
CDK 4/6 inhibitors		0.200
Ribociclib	74.4%	
Palbociclib	31.9%	
Endocrine agent combined with CDK 4/6 inhibitors		0.558
Letrozole	64.1%	
Fulvestrant	73.4%	
Metastatic sites		0.280
Non-visceral	72.9%	
Visceral	53.1%	
Biopsy to evaluate PR percentage		0.124
Primary lesion biopsy	78.4%	
Recurrent lesion biopsy	63.7%	
Adjuvan ET		0.697
No	68.4%	
Yes	64.1%	
Adjuvant endocrine agent		0.440
AI	65.3%	
Tamoxifen	63.8%	
Endocrine resistance		0.312
Yes	56.7%	
No	70.9%	
Type of endocrine resistance		0.408
Primary	64.6%	
Secondary	49.2%	

OS: Overall survival, HER2: Human epidermal growth factor receptor 2, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitör, NE: Non-estimated, *Significant

Table 4. Cox regression model for predicting the independent factors for PFS

	HR (95% CI)	p-value
Grade		
Grade 1	Ref	
Grade 2	2.15 (0.50-9.20)	0.302
Grade 3	2.79 (0.63-12.40)	0.177
PR status		0.040*
Low PR expression	Ref	
High PR expression	0.60 (0.36-0.98)	
Ki 67 index-%		0.140
≤20%	Ref	
>20%	1.50 (0.88-2.58)	
Metastatic sites		0.126
Non-visceral	Ref	
Visceral	1.44 (0.90-2.30)	
Biopsy to evaluate PR percentage		0.096
Primary lesion biopsy	Ref	
Recurrent lesion biopsy	1.93 (0.89-4.17)	
Adjuvant ET		0.725
No	Ref	
Yes	0.87 (0.40-1.89)	

PFS: Progression-free survival, HR: Hormone receptor, ET: Endocrine therapy, PR: Progesterone receptor, *Significant

Prat et al.[9] found that PR expression is prognostic in luminal A disease, with 20% being the most appropriate cut-off value. In a study, the group with PR <20% and Ki-67 ≥20% was associated with a higher malignancy grade, and these patients were shown to benefit more from chemotherapy. Thus, PR and Ki-67 status are believed to be beneficial in predicting prognosis and determining the most effective treatment strategy in ER-positive/HER2-negative breast cancer.[19] In a different study, patients with ER-positive/PR-negative tumors obtained similar poor outcomes as triple-negative tumors, and particularly in tumors with this tumor biology, chemotherapy has been shown to provide better survival benefits, especially in node-positive tumors.[12]

For CDK 4/6 inhibitor-based therapies, ongoing research investigates parameters such as PIK3CA, ESR1, SMARCA4, PDK1, and many others as potential predictive markers. However, as of now, no other biomarker besides ER expression has been identified to predict treatment for CDK 4/6 inhibitors.[20,21] This ongoing research keeps our field dynamic and engaging.

PALOMA-3 is a randomized study comparing the combination of palbociclib and fulvestrant with placebo and fulvestrant combination in patients with HR-positive/HER2-negative ABC who have previously not responded to prior ET.[22] Although the study demonstrated improved PFS and objective response rates with the combination of palbociclib

and fulvestrant, enhanced quality of life, and a favorable toxicity profile, no specific biomarker to predict response or benefit was identified in the final analysis.[23] A study using data from PALOMA-3 to identify biomarkers that could predict the long-term benefit of palbociclib and fulvestrant showed that the ER level had no impact on treatment duration. In patients with high PR levels, it was demonstrated that long-term responses occurred.[24]

In a study evaluating predictive and prognostic factors in patients with HR-positive ABC receiving the combination of palbociclib and letrozole, the mPFS was found to be 12.99 months in PR-negative tumors and 20.05 months in ER and PR-positive tumors (p:0.046).[26] In a pooled analysis by the FDA[7], with CDK 4/6 inhibitors plus ET, mPFS was found to be 27.5 months (95% CI; 18.2–29.5) in PR-negative patients and 29.1 months (95% CI; 26.2 to NE) in PR-positive patients. In this study, positive ER status was considered the best biomarker for predicting the treatment benefit of CDK 4/6 inhibitors, and PR was thought to have no prognostic value. In another study evaluating the clinical impact of CDK 4/6 inhibitors, subgroup analysis showed that in the palbociclib group, the 5-year PFS was 22.66% in PR-positive patients and 21.07% in PR-negative patients, demonstrating that PR status did not affect survival.[26] The PARSIFAL study presented at ASCO 2020 demonstrated that PR and Ki-67 levels significantly influenced the benefit of palbociclib and aromatase inhibitor (AI) therapy. Patients with low PR and high Ki-67 levels were shown to benefit less from the combination of palbociclib and AI. Palleschi et al.[27] found that PFS was inversely related to Ki-67 levels but not PR status in patients receiving palbociclib and ET.In a retrospective analysis performed by Shao et al.,[28] a cohort treated with the combination of palbociclib and AI achieved a longer PFS in patients with PR values ≥20% compared to those with <20% (not reached vs 5.8 months; p=0.012).

In our study, the mPFS was 23.13 months (95% CI; 15.67-30.59) for patients with low PR expression and 34.66 months (95% CI; 24.27-45.05) for patients with high PR expression (p:0.002). In patients with Ki-67 levels ≤20%, mPFS was NE, while for those with Ki-67 levels >20%, the mPFS was 24.08 months (95% CI; 18.96-29.21) (p:0.004). Thus, we obtained results supporting studies suggesting that PR and Ki-67 levels predict response to CDK 4/6 inhibitors**.**

Tang et al.[26] investigated whether PR expression affected survival outcomes in patients receiving CDK 4/6 inhibitors. mPFS was found to be 38 months in ER-positive/PR-positive tumors and 19.2 months in ER-positive/PR-negative tumors (p=0.0038). In the ribociclib group, the mPFS was 44 months in ER-positive/PR-positive tumors and 10.1 months in ER-positive/PR-negative tumors (p:0.0014). In the palbociclib group, the PR status did not affect survival, and the 5-year PFS rates were 22.66% in PR-positive tumors and 21.07% in PR-negative tumors.

Our study revealed a significant difference in mPFS between patients with high PR expression and those with low PR expression in both the ribociclib and palbociclib treatment groups. Specifically, patients with high PR expression treated with ribociclib demonstrated an mPFS of 35.61 months (95% CI; 25.55-45.68) compared to 23.85 months (95% CI; 12.84-34.86) for those with low PR expression (p=0.034). Similarly, in the palbociclib group, a significant difference in mPFS was observed (NE vs 16.99 months (95% CI; 5.09-28.89), p=0.024) between high and low PR expression groups. In their study, Tang et al.[26] found that both palbociclib and ribociclib were associated with lower mPFS in PR-negative tumors. However, in our study, while there was a difference in mPFS with palbociclib in patients with PR low and high expression, no such difference was observed in those treated with ribociclib. Several factors may contribute to these discrepancies, including limitations in sample size, differences in molecular characteristics beyond PR status, pharmacokinetics and pharmacodynamics of the drugs, genetic variations affecting treatment response, duration of post-treatment follow-up, patient adherence to treatment, and whether the disease is de novo or recurrent. Further comprehensive studies are needed to evaluate whether these results are statistically significant or coincidental.

Limitations

This study is subject to several limitations. Firstly, its retrospective design introduces potential biases and a lack of standardization in data collection. The sample size may be insufficient, particularly for subgroup analyses. Missing data, a common issue in retrospective studies, may also impact the findings. Furthermore, as the study was conducted at a single center, the generalizability of the findings is limited and warrants further validation in diverse patient populations. The short follow-up duration poses a limitation, especially for assessing long-term outcomes such as median OS. The evaluation of pathology specimens by a single pathologist represents a potential source of subjectivity. Technical factors related to PR assessment, including tissue irregularities, staining inconsistencies, antibody selection, and microscope settings, may have introduced variability in the results. The lack of biopsy data from recurrent lesions in approximately half of the patients limits our understanding of disease progression and treatment resistance mechanisms. Finally, the absence of newer-generation CDK 4/6 inhibitors, such as amebasiklib, due to limitations in institutional reimbursement policies, the potential deviations from standard treatment protocols in patients' received therapies, and the lack of assessment of treatment adherence represent additional limitations that should be considered.

Approaches are being investigated to identify patients likely to benefit from single-agent ET in the first line for ABC ER-positive/HER2-negative tumors, thereby avoiding exposure to the toxicities of CDK 4/6 inhibitors. However, ER positivity is currently the only established biomarker for identifying breast cancer patients who may be candidates for CDK 4/6 inhibitor therapy. The use of existing biomarkers and the development of new ones are crucial for identifying these patients.

CONCLUSION

In this study, the potential predictive role of PR expression on the response to CDK 4/6 inhibitor therapy was investigated in patients with ER-positive/HER2-negative metastatic breast cancer. A significant association was found between high PR

expression and prolonged PFS. Similarly, in the subgroups treated with ribociclib and palbociclib, patients with high PR levels achieved significantly longer mPFS. Additionally, lower Ki-67 levels were found to be associated with longer PFS. These results suggest that integrating PR and Ki-67 into clinical practice may contribute to the personalization of treatment strategies. However, given the retrospective nature of the study, the limited sample size, and its single-center design, the findings need to be validated in larger, prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

Received approval from the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.02.2024, Decision No: 2024-02/04).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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